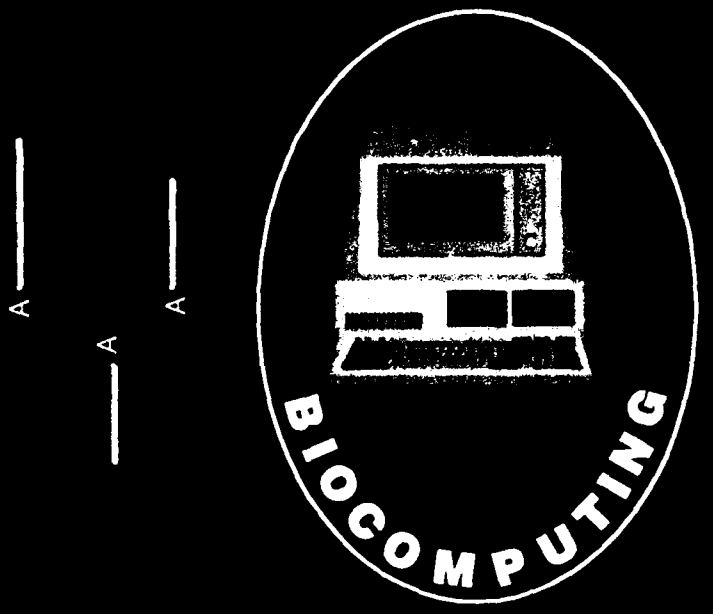
SIZING-UP

OLECULAR

LECTRONIC

EVICES



July 1990

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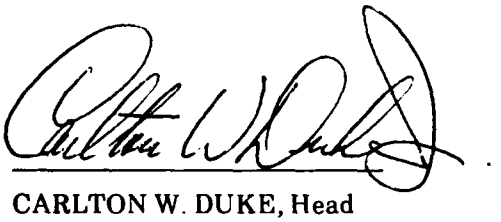

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SIZING-UP MOLECULAR ELECTRONIC DEVICES

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An emerging technology currently listed on the Department of Defense (DoD) Critical Technologies list is *biotechnology*. One aspect of this broad technology that is of interest to the Navy is organic or molecular computing. This *new field* offers great promise in the area of computing power if we are able to successfully build on recent research efforts with technology development and engineering applications to further the state of the art. Before we discuss the nature of molecular computing, we will consider the motivation and context for such a technology.

MOTIVATION AND CONTEXT

The characteristics and composition of the 21st Century Navy is an area of study at the Naval Surface Warfare Center (NAVSWC). Some of the questions are

- With global political and economic changes, what will the Navy's future missions be?
- Where will the US Navy ships operate?
- What type of ships will be required?
- What will their Combat Systems look like?
- What sensor and weapon suites will they need to carry?
- What role will Space play?
- What will the ship's crew look like?
- Will robots become a mainstream?

A first cut at answering some of these questions can be found in NAVSWC AN 90-131, *Surface Warfare Vision—Second Progress Report*.[1] Simply stated, the future Navy will be required to operate globally and cover a spectrum of responses from drug interdiction and policing peacetime operations to all-out conventional and possibly even nuclear war. The Navy must be equipped to respond in heavily populated areas of the world that have dense commercial shipping and air traffic as well as in open-ocean environments.

Thus, future ship systems must possess *sophisticated information processing capabilities* that can discern genuine threats from nonthreats or decoys and do this instantaneously so that the Commanding Officer can reflex his system with the appropriate response. In this complex world, after sorting out threats from nonthreats, a range of responses must then be considered from nonlethal evading and warnings through partial damage to total destruction. This represents a far more complicated range of choices than the present-day *shoot or don't shoot*.

NATURE OF MOLECULAR COMPUTING

Molecular computing is a novel technology that offers promise to meet this requirement for sophisticated information processing packaged in the space/weight limitations imposed by Navy ships. A molecular computer is an information processing system that uses organic or biomolecules to sense, transform, and output signals or data.[2] Some of the more impressive features of biomolecular computers are

- Their potentially very small size—5 to 100 nm for each component device.
- Their incredibly fast speed—molecular switches are >1000 times faster than silicon or gallium arsenide switches. They operate in the subfemtosecond timescale—10^{-15} s or one quadrillionth of a second. That is about 200,000 times faster than the switches in your personal computer (PC).[3]
- Their innate adeptness at pattern recognition.
- Their adaptability.

These features open an unusual view of computing systems that is non-Von Neumann, nonserial, and nonsilicon.[2]

A-1

Other terms commonly used in this field are *nanocomputing* and *molecular electronic devices*. They represent slightly different perspectives on the same basic subject. Eric Drexler, who was at the Massachusetts Institute of Technology (MIT) and is now a visiting scholar at Stanford, coined the term *nanotechnology*. It refers to building machines from the atoms up. Drexler studied under the godfather of nanotechnology, the late Dr. Richard Feynman. Dr. Feynman won the Nobel Prize in 1965 for his contributions to the foundations of molecular technology while working at Cal Tech.[4] Drexler's book, *Engines of Creation*, published in 1986 is a good source of information on nanocomputing.

MOLECULAR ELECTRONIC DEVICES (MEDs)

Molecular Electronic Devices (MEDs) is a term coined by Dr. Forrest Carter during his work in the early 1980s at the Naval Research Laboratory (NRL). MEDs are very different from Artificial Intelligence, Expert Systems, and Artificial Neural Nets. These technologies use digital and analog devices to mimic human intelligence, knowledge, and information processing. MEDs use organic materials and biochemical processes in the actual construction of electronic devices like diodes, switches, and transistors. These materials are at the molecular level—on the order of Angstroms (10^{-10} m) and nanometer (10^{-9} m) dimensions.

A typical *species* of biological molecule used to build MEDs is *proteins*. They are the fundamental building blocks for most biological structures (everything from ultracellular organelles to muscle tissue in animals). In addition to their variety of form, proteins also perform variegated functions that range from basic structural support of form (e.g., the keratin in our toenails and hair) to ultrasophisticated parallel information processing as seen in systems such as the central nervous system or the lymphatic system.

Within the lymphatic or immune system, there are proteins that function as various messenger complexes and respond to invading bacteria and viruses. The immune system uses a sophisticated cascading sequence of interlacing enzyme-substrate reactions to *build* intricate complexes of different protein components that infiltrate and destroy infected cells. An *enzyme* is a term used to describe a special type of protein that acts as a biological catalyst. The enzyme acts on one or more specific substrate molecules and converts them into products of a different molecular form.

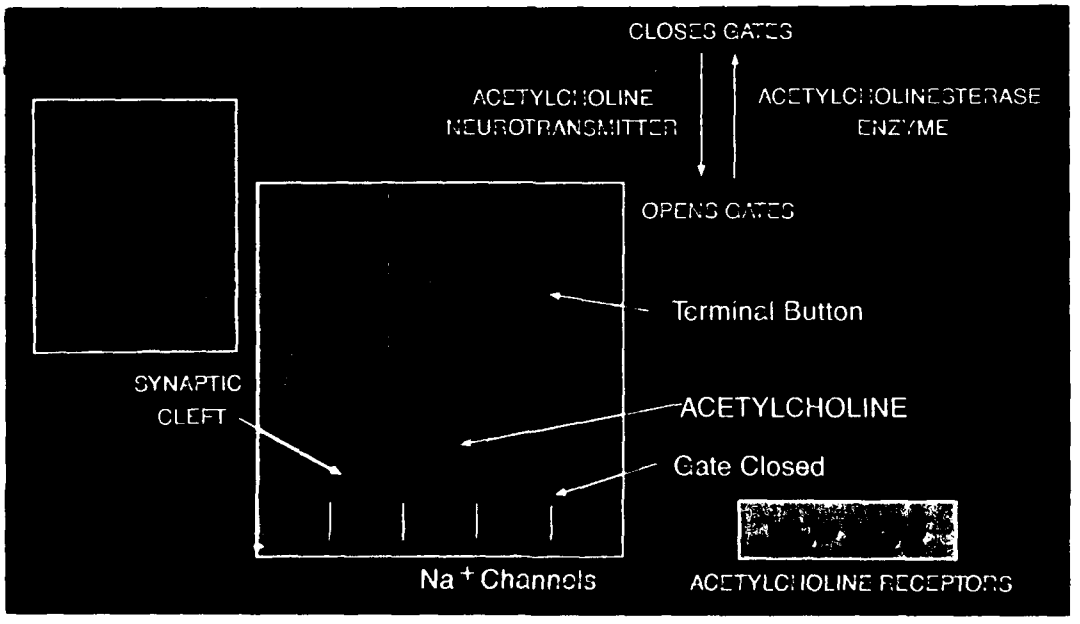

Figure 1. Neuromuscular Junction

To illustrate the degree of complexity involved in enzyme-substrate reactions, we examine the sequence of events required for a simple muscle contraction. The left-most box in Figure 1 depicts a single neuron (nerve cell) at the junction of skeletal muscle tissue; hence the term *neuromuscular junction.* The center box shows a magnified view of this junction. The figure shaded in pink with the bulging terminal buttons is a specialized structure on the ends of the neuron. The nerve impulse travels down the axon of the nerve cell to these terminal buttons that are rich with vesicles of the neurotransmitter, acetylcholine. The polarity of the membrane enveloping the terminal buttons affects the migration of these vesicles toward the synaptic cleft where they release acetylcholine (yellow) into the synapse.

An acceptor molecule called the *acetylcholine receptor* (blue), which is located on the surface membrane of the muscle cells (in red), binds with the acetylcholine and subsequently undergoes conformational changes to *open* ion channels or gates for the Na^+ and $K+$ to flow through into the muscle tissue and trigger muscle contraction. In the reverse reaction, the enzyme acetylcholinesterase is released to break down the acetylcholine, which in turn causes a reverse conformational change in the acetylcholine receptor and in effect *closes the gates* so that ions cannot flow through and the muscle cell relaxes.

The acetylcholine molecules together with the acetylcholine receptor and acetylcholinesterase enzyme operate in conjunction with the specialized nerve and muscle ultrastructure to, in effect, behave like intelligent switches, *sensing* from the environment when to open the gate and permit ions to flow through and also *sensing* when to close the gates and stop ion flow. This occurs on a unique scale of size. These structures are on the order of 5 to 10 billionths of a meter across.

Dr. Conrad of Wayne State University uses the term *molecular dynamics* to describe the combination of physical and chemical reactions that involves spatial, temporal, and motile actions that occur at this level. These biomolecules are small enough to scan another molecular object through thermal motion for recognition yet large enough to form molecular complexes with objects that have a complementary shape. This is the basis of enzyme-substrate reactions commonly referred to as lock-and-key interactions.[2]

MEDs built using such proteins would derive their functional performance from their *shape* and *molecular dynamic motion.* First, the function of a protein is implicit in its structure; e.g., the molecular protein hemoglobin is specifically structured to perform its function of transporting molecules of oxygen. Secondly, hemoglobin and other protein molecules are sensitive to second- and third-order localized molecular physiochemical conditions so that they know when to activate or deactivate their *program.* Hence, hemoglobin *senses* from its environment within the red blood cell when to release oxygen (at the capillaries) and when to absorb oxygen (at the bronchiole alveoli).

BIOMOLECULES

Four of the features of biomolecules that researchers hope to exploit are their small size, complexity, low input power, and adaptability.

Small Size

Consider size—how small is a nanometer? Figure 2 shows the comparative size of a current state-of-the-art digital chip (about 1 cm^2) with that of a red blood cell (RBC) (about 7 μm in diameter) and a hemoglobin molecule (about 5 nm in diameter). A hemoglobin molecule approximates the lower end of the scale for the size of MED components; i.e., about 5 to 100 nm. The width of this line is about 250 micrometers: _____ So, about 40 RBCs could fit across the thickness of that line. We can fit 280 million hemoglobin molecules inside a single RBC. Roughly 11 billion devices about the size of a hemoglobin molecule could fit across the thickness of that line!

The molecules that will be used to build MEDs (primarily proteins) will be similar in size and structure to the hemoglobin molecule, which consists of about 10,000 atoms of H, O, N, C, and S arranged into some 500 amino acid subunits. Their small size in no way limits their complexity of structure and function.

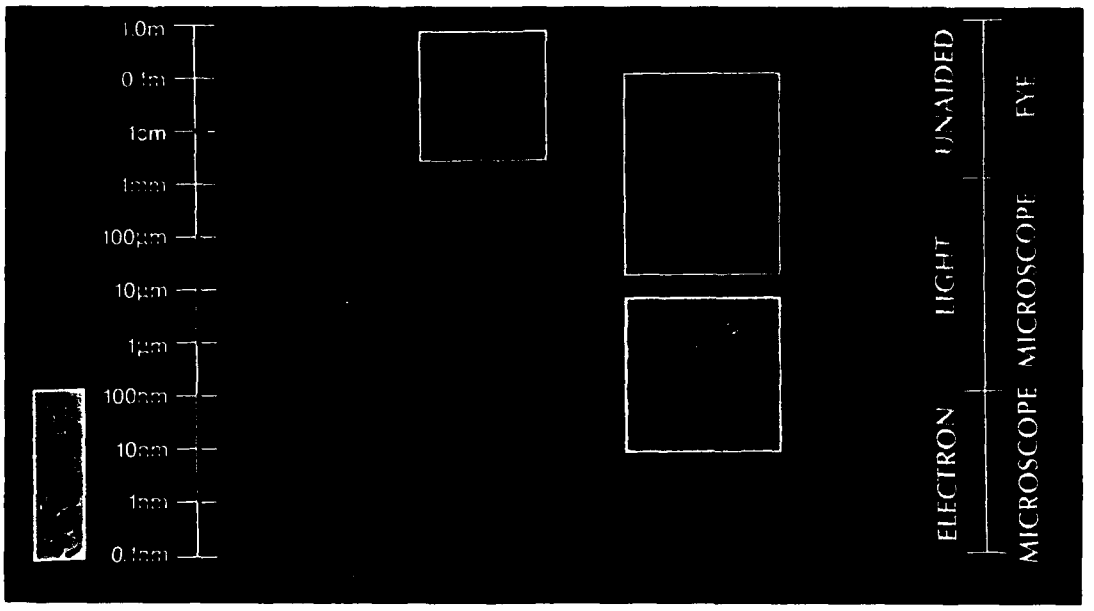

Figure 2. Sizing-Up Molecular Devices

Complexity of Structure

To better understand how electronic devices can be constructed out of biomolecules such as proteins, it is necessary to understand exactly what a protein is and the properties it possesses. By definition, a protein is a complex macromolecule folded into a specific structure by chemically linked amino acid subunits that enable it to perform a specific function.[5]

Hemoglobin is basically four strands of amino acids, each of which is termed a *polypeptide*. These four polypeptides form a complex structure of four subunits. The complexity of structure is what allows the hemoglobin molecule to have the aptitude to execute its specific function of transporting oxygen. In doing so, this protein, as well as many others, has the capability to undergo *conformational changes*. When an oxygen molecule is bound to hemoglobin, the protein is in one conformation. When the oxygen is released, the hemoglobin undergoes a conformational change to expose the oxygen molecule and release it. Therefore, this protein can exist in two different conformations or states. A comparison could then be made between the protein and the binary code—lending itself to the application of memory storage.

Although these molecules are incredibly small, they have a high level of structure associated with them. It is this high degree of complex structure that allows these molecules to perform their specific functions. This complexity can be illustrated by the folding process that each polypeptide must undergo to become a protein with a function. Specifically, hemoglobin will be described (Figure 3).

Figure 3. Structural Complexity

The protein begins as amino acids that are chemically linked together as coded for by the DNA. Hemoglobin contains 500 of these amino acids. At this point, the protein is in its primary structure. As the amino acids begin to form the polypeptide strand, they chemically interact with other amino acids around them to form a helical structure called the secondary structure. Intrachain interactions then form to cause the helix to fold in a way that is characteristic of only that specific sequence of amino acids. The protein now exists in its tertiary structure. If the protein is one that requires more then one subunit to attain its functionality, it then binds with other subunits to take on its final quaternary structure. As can be seen by the illustration in Figure 3, hemoglobin is one such protein. This protein now has the capability to perform its function. No other protein can perform the function of transporting oxygen in a similar manner as hemoglobin.

This description elucidates the fact that a protein does not need to be programmed in order to function—its function is inherent in its structure. One fundamental rule that permeates all biological systems is the intimate relationship between structure and function or morphology and physiology. These features are so inextricably intertwined that one does not exist without the other.

Some of the complex functions proteins perform within biological systems that are being isolated for use in MEDs include signal transport, switching, memory, and logic. A good example of a protein that performs both signal transport and switching functions is the nicotinic acetylcholine receptor (introduced previously). The receptor both transports the nerve impulse from the nerve to the muscle cell as well as acting as a switch—it closes the ion channel when the muscle cell has reached its threshold. This will be described in detail later.

Although only four are mentioned, there are many more protein functions that could be exploited. For example, it only takes one amino acid alteration to completely change the structure and function of any given protein. This characteristic endows the protein with its dynamic nature. You can imagine the many different possible amino acid combinations. To be exact, there are 20 different amino acids and 20^{300} or $2x10^{1310}$ different possible combinations (different possible proteins), all with different specific functions. If all of these functions could be exploited in MEDs, an incredibly superlative system could be devised.

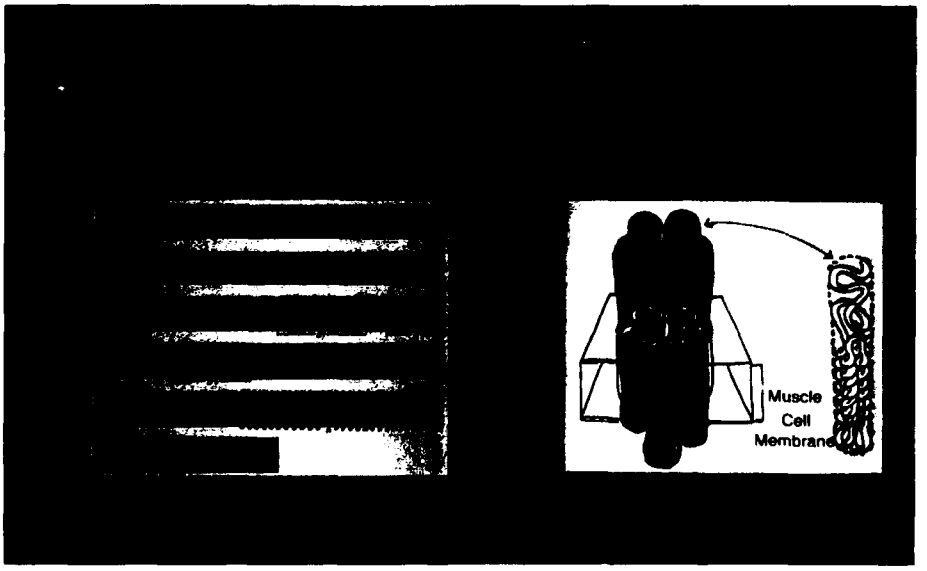

Figure 4. Functional Complexity

This is indicative of another very important characteristic of proteins—their specificity. The *exact* order of amino acids and their characteristics is what determines the specific structure of the protein. This specific structure defines the protein and determines its exact form or shape and function. Think of a lock and key. If you change the configuration of the key, it no longer fits the lock and cannot perform its function of unlocking. Therefore in proteins, the precise molecular structure determines the particular function that they will perform. Any alteration in structure results in a similar alteration of function.

Complexity of Function

The discussion will now shift to the complexity of function that these proteins perform. The nicotinic acetylcholine receptor exemplifies complexity of function (Figure 4). This receptor is found embedded in the plasma membrane of enervated muscle cells. Where hemoglobin has four subunits, the acetylcholine receptor has five: two alpha; one beta; one gamma; and one delta. Each of these five subunits represents the tertiary structure of the protein. The quaternary structure of the polypeptide is described by the arrangement of five alpha helicies with hydrophobic and hydrophillic portions that are bound together in a circular manner of alpha, beta, alpha, gamma, delta so that a *channel* is formed through the middle.

When an impulse traveling along a nerve reaches the terminal button, acetylcholine is released from the terminal button into the synapse, which is the space between the nerve and the muscle cells. To transport the signal, the acetylcholine molecules traverse the synapse and bind to the *alpha* subunits on the many receptor proteins found on adjacent muscle cells. This binding causes a conformational change in the receptor to open the channel and allow ions to flow through and ultimately stimulate the muscle. In this way, this protein is acting as a signal transporter. When the muscle cell has reached its threshold, the protein recognizes this and undergoes a reverse conformational change to close the channel. The protein is then sensing its environment and acting as a switch.[6]

CONVENTIONAL VS BIOMOLECULAR COMPUTERS

A review of the complexity of proteins can be seen in a comparison of conventional and biomolecular computers. A conventional device is structurally programmable (i.e., it operates on a string of symbols or instructions). A biomolecular device's program is inherent in its structure. As a result, a conventional machine computes symbolically. Because proteins are performing the functions in a biomolecular machine, the processing is physical and dynamical. Therefore, in a conventional computer, the program depends on human effort and intelligence. In a biomolecular computer, programming depends on evolution by variation and selection.[2] Dr. Conrad provides in-depth comparisons between conventional digital computing and molecular computing in [2] and to a greater extent in *On Design Principles for a Molecular Computer* [7].

A final impression the authors wish to leave with the readers is that Molecular Computing is **real**. At John Hopkins University/ Applied Physics Laboratory (JHU/APL), when a laser light is applied to a thin film of tetracyanoquinodimethane (TCNQ) and copper (Cu), it binds or unbinds the Cu and switches the film from conducting to nonconducting.[7] Dr. Robert Birge at the Syracuse University Center for Molecular Electronics (CME) is constructing a high-speed optical molecular random access memory (RAM) using bacteriorhodopsin. Pulses of laser light induce conformational changes of form that act as a toggle switch for reading or writing data to the molecular material. Dr. Birge projects a 2-ns worst switching time and a 3-ps cycle time.[3] The CME designed a molecular NAND gate that is 4 nm in diameter and fires in subfemtoseconds with a cycle time of 3 ps—that is 10,000 times faster than the silicon gates in a Cray supercomputer![8]

Dr. Felix Hong, Wayne State University, is working on a prototype MED using bacteriorhodopsin embedded in Langmuir-Blodgett films. Interestingly, both Hong and Conrad propose that the key to molecular and chemical electronics is to take advantage of the quantum and thermal *side-effects* experienced at this level of micromanipulation vice trying to

eliminate them. *What are side effects from the standpoint of conventional computing is the essence of biological information processing.*[2]

As further evidence to support the potential for a plethora of molecular devices, Tien et al., experts in bilayer lipid membranes (BLM) at Michigan State, propose building artificial BLM-based MEDs.[9] Table 1 provides a sample of the devices and corresponding biomaterials.[10] Tien's paper also provides a sample of the biological molecular transducers (Table 2).[10]

Table 1. Molecular Electronic Devices*

Devices	Biomaterial
Molecular Wire	Conducting Polymers
Molecular Resistor	Polyacetylene, Polypyrrole
Molecular Capacitor	Lipids and Hydrocarbons
Molecular Switch	Lipid Bilayers
Molecular Diode	Doped BLM
Molecular Rectifier	TCNQ BLM
Photosensitive Elements	Semiconducting BLM
Push-Pull Compounds	TPP-Quinone (P-Q)
Chemical Sensors	Doped BLM
Energy Transducers	Biofuel Cells

*Modified and adapted from Reference 10, Table 3, p S18

INTERDISCIPLINARY APPROACH

Having given a brief overview of both the technical depth and breadth this technology encompasses, there is one aspect the authors wish to stress that is crucial to furthering the development of biocomputing—the requirement for an interdisciplinary approach to biocomputing (Figure 5). At this stage of development, the disciplines include Biology, Chemistry, Physics, Electrical Engineering, Computer Science, and Mathematics. In the future, this list may grow; however, it is highly unlikely that it will shrink.

The knowledge from each area is equally crucial in creating a viable organic computer. Therefore, the area of concern lies in orchestrating these disciplines to benefit from one another's expertise. To be successful, these areas must cross-collaborate. As with any emerging technology, the ultimate advantages to be gained from a viable product can only be suspected; but if these disciplines can begin to collaborate for this purpose, the ultimate products and advantages may be far greater than we can currently imagine!!

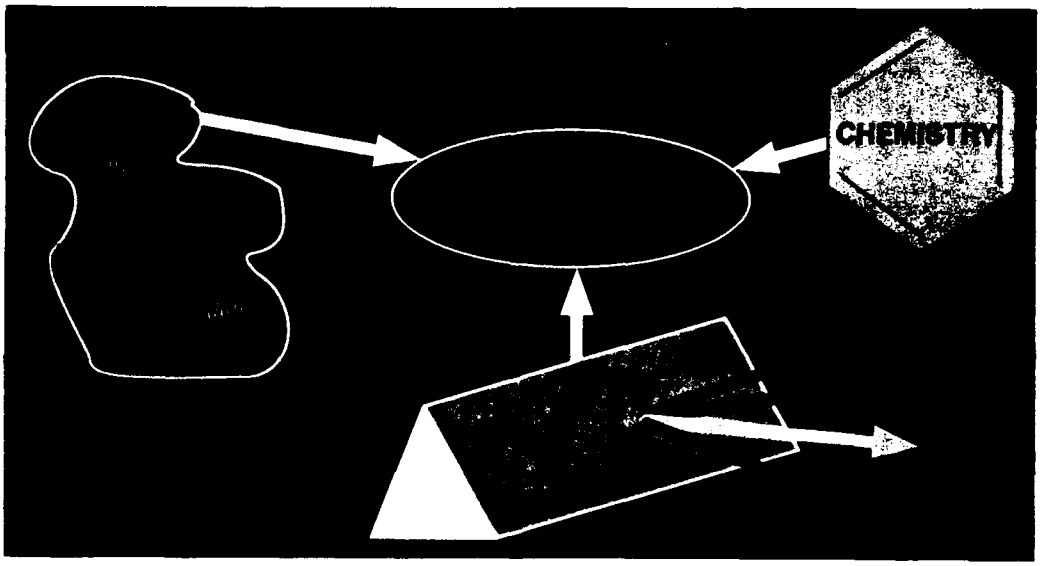

Figure 5. Technology Engineering

Table 2. Nature's Molecular Electronic Transducers*

Functional Unit	Membrane	Transduction
Chloroplast	Thylakoid	Light ——> Light ——> Electrical ——> Chemical
Mitochondrion	Cristae	Chemical ——> Chemical
Retina	Rod and Cone Sac	Light ——> Electrical
Nervous System	Nerve Axon	Ion Concentration Gradient ——> Electrical
Cell	Plasma	Chemical ——> Osmotic
Inner Ear	Tectorial	Acoustic ——> Electrical
Muscle	Actomyosin	Chemical ——> Mechanical
Vocal Cord	?	Mechanical ——> Sonic
Firefly	Plasma	Chemical ——> Light
Electric Eel	Electroplex	Chemical ——> Electrical

*Modified and adapted from Reference 10, Table 1, p. S2

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